# Clinical Medicine

## 'Pseudoseptic' Arthritis in Patients With Rheumatoid Arthritis

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***It is generally recognized that patients with rheumatoid arthritis are at greater risk than the general population for the development of bacterial joint infection. It is not usually appreciated, however, that such patients may present with a clinical syndrome that mimics septic arthritis in most respects except that all cultures are consistently negative and antibiotics are not essential for treatment. We report our experience with five cases of "pseudoseptic" arthritis in patients with rheumatoid arthritis and suggest an approach for management.***

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Patients with rheumatoid arthritis are at greater risk for bacterial infection of joints than the general population.[1-5] Certainly when a patient presents with disproportionate pain and swelling in one or more joints, especially if accompanied by the abrupt onset of systemic features such as fever and chills, the primary objective is to exclude an infectious process. The early correct diagnosis of joint infection in patients with rheumatoid arthritis may be difficult because both the preexisting joint disease and the anti-inflammatory drugs used in treatment may obscure or alter the presentation of the joint infection. In addition, more than one joint can be infected. Thus, the clinical presentation of septic arthritis in patients with rheumatoid arthritis may be atypical or incomplete.

We have recently seen five patients with rheumatoid arthritis who presented with clinical and laboratory findings that were highly suggestive of bacterial infection of the joints, but synovial fluid and blood cultures were sterile. These patients were admitted to hospital and two were given extended antibiotic treatment for "culture-negative septic arthritis." We now recognize a clinical syndrome in such patients that mimics septic arthritis. We here report these observations and suggest an approach to management.

### Patients

Five patients with classical rheumatoid arthritis are included in this description. For illustrative purposes, two brief patient reports (cases 1 and 3) are presented.

*Case 1*

The patient, a 29-year-old man with rheumatoid arthritis of 14 years' duration, was admitted to hospital with a history of fever and acute painful swelling of the left knee for 24 hours. His oral temperature was 38.3°C (100.9°F). On general physical examination there were no remarkable findings except for the changes of rheumatoid arthritis. His left knee was swollen, erythematous and had a palpable effusion in addition to significant synovitis. The synovial fluid nucleated cell count was 35,000 per μl with 89% polymorphonuclear leukocytes (PMNs) and the glucose concentration was 10 mg per dl. A Gram's stain and polarized microscopy for crystals were negative. A presumptive diagnosis of bacterial infection of the joint was made and treatment with parenteral nafcillin sodium and cefazolin sodium, as well as supplemental prednisone, was instituted. The fever resolved within 24 hours and the joint pain, swelling and warmth abated. Despite the absence of bacterial growth in cultures of synovial fluid and blood, antibiotic treatment and daily needle drainage of the knee were continued, and the cultures were consistently negative for bacterial growth. After 21 days of antibiotic treatment, the blood leukocyte count dropped to 2,700 cells per μl with 3% PMNs. Leukopenia due to nafcillin therapy was suspected and the antibiotic therapy was discontinued. He continued to do well and was discharged from hospital when his leukopenia resolved.

Four months later he was readmitted with fever, chills and pronounced swelling, tenderness, warmth and erythema of the

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left knee. The results of a physical examination were not changed from his previous admission findings. The synovial fluid nucleated cell count was 50,000 cells per μl with 91% PMNs and a glucose concentration of 6 mg per dl. Despite a Gram's stain that showed no bacteria, a regimen of parenteral gentamicin sulfate and cefazolin was initiated along with an increase in the prednisone dosage from 4 mg a day to 20 mg a day. Within 48 hours, he was afebrile and the acute arthritis of the left knee had resolved. The synovial fluid nucleated cell count was 34,000 cells per μl with 81% PMNs. The antibiotic therapy was discontinued and he has shown no evidence of infection in 48 months of observation.

*Case 3*

The patient, a 37-year-old man with rheumatoid arthritis of ten years' duration, had a three-week generalized "flare" in his joint disease. He was admitted to hospital with a 24-hour history of severe redness, heat, swelling and pain in both wrists associated with rigors and fever. His only therapy was the administration of naproxen, 750 mg a day. On physical examination there was synovitis of several joints, rheumatoid nodules and both wrists were erythematous, warm, swollen and extremely tender. His oral temperature was 37.7°C (99.9°F). The synovial fluid from the wrist had 98,000 nucleated cells per μl with 88% PMNs and a glucose concentration of less than 10 mg per dl. Crystals were not found and a Gram's stain was negative. Synovial fluid cultures were done for *Neisseria,* aerobic and anaerobic bacteria, mycobacteria and fungi. Conventional blood cultures were done. The peripheral blood leukocyte count was 13,000 cells per μl with 33% PMNs.

There was no evidence for an associated infection by history or physical examination and he was given nafcillin parenterally. Within 24 hours he was afebrile, his acute arthritis in the wrists abated and cultures of synovial fluid yielded no growth. Antibiotic therapy was discontinued, he remained well, except for his rheumatoid arthritis, and was discharged from hospital.

Three months later, he had a shaking chill and presented with the abrupt onset of painful swelling in his right wrist. On physical examination, findings of generalized rheumatoid arthritis were unchanged except for warmth, pronounced swelling and severe tenderness and pain of the right wrist. A synovial fluid specimen from the wrist had a nucleated cell count of 129,000 cells per μl with 90% PMNs. No crystals were seen on polarized microscopy and a Gram's stain was negative. Nafcillin and gentamicin were given and within 24 hours the acute arthritis in the wrists resolved. When cultures of synovial fluid and blood specimens showed no growth, the antibiotic regimen was discontinued and he was discharged. He has remained well except for his chronic rheumatoid arthritis for 54 months.

*Comments*

Five patients with rheumatoid arthritis had one or several episodes of acute inflammation in one or more joints that were associated with fever, chills or both in four cases (Table 1). The duration of illness was from 12 to 48 hours when initially evaluated. Large joints involved in decreasing frequency were the knees, wrist, ankle, elbow and shoulder. The peripheral joints of the hands and feet were not noted to be unusually inflamed in these patients.

All patients had substantial tenderness, painful motion and an effusion in the involved joint. Erythema or warmth of the involved joint or both were recorded in six of ten episodes and systemic fever was present in seven. Peripheral blood leukocytosis was usually present and, when measured, the Westergren erythrocyte sedimentation rate was elevated.

The synovial fluid findings were impressive, with nucleated cell counts of greater than 50,000 cells per μl in all but one instance. A notable preponderance of PMNs was also seen except in one patient (patient 2) whose synovial fluid nucleated cell count was 96,400 cells per μl (Table 1). Crystals were not identified in the fluids and a Gram's stain was negative in all. Cultures failed to yield growth of bacteria, mycobacteria and fungi in all patients. The synovial fluid glucose concentration was often greatly decreased.

In all patients, there was a rapid resolution of the acute joint symptoms. This response is difficult to assess because increased doses of prednisone were given in six episodes. On the basis of a presumptive diagnosis of bacterial infection of the joint, antibiotics were given for eight of the ten episodes. In two patients, these were continued for two weeks or longer despite negative synovial fluid and blood cultures. In the other patients, the antibiotic therapy was promptly stopped when synovial fluid cultures showed no growth. In two episodes, antibiotic treatment was withheld pending positive cultures.

A review of these patients failed to elicit a cause for the

TABLE 1.—*Selected Clinical and Laboratory Variables in Patients With Rheumatoid Arthritis Who Were Admitted With the Diagnosis of Bacterial Infection of Joints*

| Patient | Age yr | Sex | Episode | Admission Temperature °C | Peripheral Leukocyte Count per μl | ESR mm/hr | Rheumatoid Factor Titer | Synovial Fluid Findings: Nucleated Cell Count per μl | Synovial Fluid Findings: % PMNs | Synovial Fluid Findings: Glucose mg/dl |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 29 | ♂ | 1 | 38.3 | 11,400 | 53 | 1:320 | 35,000 | 89 | 10 |
| | | | 2 | 38.5 | 11,100 | 39 | | 50,000 | 91 | 6 |
| 2 | 65 | ♂ | 3 | 37.0 | 19,300 | ND | 1:320 | 395,000 | 94 | 13 |
| | | | 4 | 38.4 | 11,600 | ND | | 96,400 | 73 | 60 |
| | | | 5 | 38.5 | 20,000 | 70 | | 60,000 | 90 | <10 |
| | | | 6 | 35.6 | 18,000 | 123 | | 113,000 | 88 | ND |
| 3 | 37 | ♂ | 7 | 37.7 | 13,000 | 33 | 1:320 | 98,000 | 88 | 6 |
| | | | 8 | 36.7 | 8,600 | ND | | 129,000 | 90 | ND |
| 4 | 64 | ♂ | 9 | 37.3 | 24,700 | ND | 1:1280 | 89,000 | 97 | ND |
| 5 | 69 | ♀ | 10 | 37.3 | 7,900 | 56 | 1:40 | 52,000 | 92 | ND |

ESR=erythrocyte sedimentation rate, ND=no data, PMNs=polymorphonuclear leukocytes

abrupt flare in the involved joints. All had classical, seropositive, nodular rheumatoid arthritis. None of these patients had clinical evidence of concomitant bacterial, viral, mycobacterial or fungal infections. The possibility of gonococcal arthritis was not considered likely as all patients and their marital partners denied extramarital sexual activity. Furthermore, there were no symptoms or signs of urethritis, cervicitis or skin lesions, and while cervical, urethral, rectal and throat cultures were not done on Thayer-Martin media, synovial fluid cultures on chocolate agar uniformly failed to yield growth of *N gonorrhoeae*. While synovial biopsies to exclude mycobacterial or fungal infection were not done, the clinical presentation, negative synovial fluid cultures for mycobacteria and fungi and the subsequent clinical course of the patients exclude these diagnoses. No crystals were seen in any of the synovial fluids and all patients had normal serum uric acid concentrations. Patient 1 has been followed for more than four years and the other patients for at least three years without evidence of disease other than rheumatoid arthritis.

## Discussion

In five patients with seropositive classical rheumatoid arthritis of long duration, we observed ten episodes of acute monarticular or oligoarticular flares that were initially considered to be bacterial infection of the joint(s). Cultures of synovial fluid and blood, however, yielded no growth and there was rapid resolution of the arthritis that appeared to be independent of antibiotic treatment. Thus, we propose that patients with rheumatoid arthritis can present with clinical and laboratory features that mimic bacterial joint infections and we have termed this syndrome "pseudoseptic arthritis."

The usual approach to these patients is to look for an associated infection or portal of entry. Appropriate cultures as indicated by these findings are done. Cultures of blood specimens are obtained and synovial fluid analysis for total and differential cell counts, crystals, glucose content and cultures for *N gonorrhoeae*, aerobic and anaerobic bacteria, mycobacteria and fungi is considered. A Gram's stain on the centrifuged fluid specimen is examined and appropriate antibiotics are given immediately based on the most likely infecting organism. When there is no evident portal of entry or concomitant systemic bacterial infection and a Gram's stain of the synovial fluid is negative, broad-spectrum antibiotic therapy is implemented if the synovial fluid nucleated cell count is high and there are greater than 90% PMNs. This approach seems reasonable in acutely ill or severely debilitated patients.

At its inception, bacterial infections of joints most often result from hematogenous seeding of the synovium. This tissue infection ultimately spreads to the joint space.[6] Thus, early infection cannot be excluded by an absence of bacterial growth from synovial fluid culture and repeated daily or more frequent synovial fluid aspiration and cultures must be done to determine infection. Faced with the dilemma of the clinical impression of bacterial joint infection, a negative synovial fluid Gram's stain and no identifiable portal of entry, antibiotic treatment is usually started immediately. Treatment is then continued pending culture results and the response of the arthritis. In the setting of no growth from cultures and rapid clinical improvement, the antibiotic regimen might be discontinued. Careful further observation is then required to ensure that incompletely treated bacterial arthritis is not present, while considering "pseudoseptic arthritis" as a likely explanation.

A major problem with this approach is to define response in a joint with preexistent rheumatoid synovitis. Successful treatment of bacterial infection of a joint is measured by rapid eradication of the infective agent as indicated by negative synovial cultures, whereas a decrease in arthritis, total synovial fluid and total leukocyte and polymorphonuclear cell counts may not be observed for up to seven or more days of treatment.[7]

An alternative approach is to consider that "pseudoseptic arthritis" could be present. If the Gram's stain of synovial fluid is negative and the patient does not have an identifiable portal of entry, concomitant infection (pneumonia, urinary tract infection and so forth), an immunocompromised state (high-dose steroids, cytotoxic or immunosuppressive drug therapy) or features of bacterial sepsis, antibiotic treatment might be delayed pending the results of synovial fluid cultures. A decision of "not to treat" is easier if a patient has had previous episodes of culture-negative arthritis. Thus, a physician will be able to avoid the use of prolonged antibiotic treatment usually recommended for nongonococcal bacterial arthritis. Conversely, if an organism is ultimately found, selective therapy can be devised. Furthermore, the adequacy of treatment can be assessed by determining serum or synovial fluid antibiotic bactericidal levels and by repeated monitoring of synovial fluid for response to therapy by disappearance of the organism in synovial fluid cultures. Based on available evidence, a delay of two to five days *early* in the course of bacterial infection of joints would not influence an ultimate successful result.[7] If the severe monarthritis or oligoarthritis persists, a repeated search for infection, including joint fluid analysis, should be diligently pursued.

The pathogenesis of this syndrome remains unexplained. As this was a retrospective study, synovial fluid counterimmunoelectrophoresis was not done, nor were bacterial peptidoglycans or microbial antigens in synovial fluid or antibodies to bacterial antigens sought.[8] While all of the patients had classical rheumatoid arthritis, there were no unique features such as vasculitis. They did not exhibit the typical rash of adult Still's disease, nor did they have lymphadenopathy, splenomegaly or other systemic manifestations.

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